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Neonatal NMDA receptor blockade alters anxiety- and depression-related behaviors in a sex-dependent manner in mice

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ABSTRACT

There is increasing evidence that *N*-methyl-D-aspartate (NMDA) receptor blockade in the neonatal period has a long-lasting influence on brain and behavior development and has been linked to an increased risk for neuropsychiatric disorders in later life. We sought to determine whether postnatal NMDA receptor blockade can affect normal development of body weight, corticosterone levels, anxiety- and depression-related behaviors in male and female mice in adulthood. For this purpose, male and female NMRI mice were treated with either saline or phencyclidine (PCP; 5 and 10 mg/kg, s.c.) on postnatal days (PND) 7, 9, and 11, and then subjected to different behavioral tests, including open field, elevated plus-maze, elevated zero-maze, light-dark box, tail suspension test and forced swimming test in adulthood. The results indicated that neonatal PCP treatment reduced body weight during neonatal and adulthood periods, and did not alter baseline corticosterone levels in both male and female mice. Moreover, this study obtained some experimental evidence showing the PCP at dose of 10 mg/kg increases stress-induced corticosterone levels, anxiety- and depression-related behaviors in males, while decreasing levels of anxiety without any significant effect on depression in female mice in adulthood. These data support the argument that neonatal NMDA receptor blockade can lead to behavioral abnormalities and psychiatric diseases in adulthood. Collectively, our findings suggest that neonatal exposure to PCP may have profound effects on the development of anxiety- and depression-related behaviors in a sex- and dose-dependent manner in mice.

1. Introduction

The neonatal period is an important neurodevelopmental stage to the understanding of the etiology and developmental trajectory of neuropsychiatric disorders such as anxiety and depression in later life. Epidemiological reports indicate that these behavioral dysfunctions are complex and multifactorial disorders involving both genetic and environmental factors (Anisman et al., 2008). It was found that anxiety is often associated with depression (Beuke et al., 2003) which is not surprising, considering the notion that these disorders share a common genetic pathway (Kendler et al., 2007; Williamson et al., 2005). There are fundamental differences between male and female in many psychological and behavioral aspects, and also the structure and morphology of the brain in both sexes are highly similar. Hence, there are consistent differences between them with subsequent important implications for each sex (Bao and Swaab, 2011; Ngun et al., 2011). For example, anxiety and depression are almost twice as common in females as in males (McLean and Anderson, 2009); however the factors mediating these differences are not well understood.

A number of recent studies have demonstrated that *N*-Methyl-D-aspartate (NMDA) receptor plays an important role in normal brain development and plasticity during early life (du Bois et al., 2009a; du Bois and Huang, 2007; Lim et al., 2012). It has been documented that the developing neurons strongly depend on NMDA receptor

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